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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/704,306 11/02/00 BECK

J PH-7032

EXAMINER

HM12/0911

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USE FILE

ART UNIT

PAPER NUMBER

1624

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/704,306

Applicant(s)

BECK ET AL.

Examiner

Rao M Uppu

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 November 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-49 is/are pending in the application.
- 4a) Of the above claim(s) 37-41 and 48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-36, 43-47 and 49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I Claims 1-36, 43-47, 49, drawn to compounds and compositions classified in classes/subclasses 546/143, 546/144, and 514/310.
- II Claims 37-41, 48, drawn to complex compositions and their methods of use, classified in class 514 and subclasses depend on the nature of additives.

The groups I and II are distinct, each from the other because of the following reasons: Group I embraces 4-(un/substituted) phenyl-1,2,3,4-tetrahydroisoquinolines having substituents at 2, 3, 7, 8, 9-positions, classified in classes 546 and subclasses 143 and 143. Groups II embrace complex compositions consisting of serotonin receptor 1A antagonists, neurokinin-1 receptor antagonists, and norepinephrine precursor(s), and their methods of use, classified in class 514 and subclasses depend on the nature additives. These groups of compounds are structurally dissimilar, made independently and used independently. They would be expected to raise different issues of patentability; for example, if a compound of Group I was anticipated, the anticipatory reference would not necessarily render obvious the other Group II or vice-versa. They are not art-recognized equivalents, as they are classified diversely in different classes (546, 514) and subclasses and require separate literature searches.

Should Applicants traverse on the ground that the groups are not patentably distinct, Applicants should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the groups unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other group.

During a telephone conversation with Applicants' attorney Mr. Kalim Fuzail on June 20, 2001 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-36, 43-47, and 49. Applicants must make affirmation of this election in replying to this Office action. The Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, withdraws claims 37-41 and 48 as non-elected subject matter from further consideration.

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims

are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Applicants numbered claims 1-27 correctly but some of the claims that followed claim 27 were misnumbered. The misnumbered claims 29, 29, 30, 31, 32, 34, and 34 have been renumbered as 28, 29, 30, 31, 32, 33, and 34, respectively. The claim numbers cited in this Office action are the corrected claim numbers.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-36, 43-47, and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Tirelli et al (J. Pharmacol. Exp. Med., 273, 7-15, 1995), Salama et al. (Br. J. Haematol., 78, 535-539, 1991), CH 538477 (1973), and DE 2062001 (1971).

Claims 1-6, 9, 16, 18, 19, 26-29, 35, 36, 43-47, 49 are rejected under 35 U.S.C. 102 (b) as being anticipated by Tirelli et al. and Salama et al. The said references teach 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (RN 67165-56-4) (see Tirelli et al.) and 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-2-methyl-7-isoquinolinol (RN 34041-52-6) (see Salama et al.), which, in turn, read on the instant claims in which the 4-phenyl-1,2,3,4-isoquinoline ring system contains substituents R¹

(methyl), R², R³ and R⁵ (hydrogen), R⁶ and R⁷ (chloro), and R⁴ (methoxy or hydroxy; respectively).

Claims 1-7, 10, 11, 15, 16, 18, 19, 23, 24, 26-29, 35, 36, 43-47, 49 are rejected under 35 U.S.C. 102 (b) as being anticipated by CH 538477. The instant claims read on compounds 4-(3-chlorophenyl)-1,2,3,4-tetrahydro-7-methoxy-2-ethylisoquinoline (RN 34048-18-5), 4-(3, 4-dichlorophenyl)-1,2,3,4-tetrahydro-2-ethyl-7-isoquinolinol (RN 34048-19-6), 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-7-methoxy-2-(1-methylethyl)isoquinoline (RN 34048-20-9), 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-2-(1-methylethyl)-7-isoquinolinol (RN 34048-21-0), 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-7-methoxy-2-(phenylmethyl)isoquinoline (RN 34048-23-2), 4-(3-chlorophenyl)-1,2,3,4-tetrahydro-2-methyl-7-isoquinolinol (RN 34154-25-1), 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-7-methoxy-1,2-dimethylisoquinoline (RN 43072-81-7), and 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1,2-dimethyl-7-isoquinolinol (RN 43072-88-4).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-36, 43-47, and 49 are rejected under 35 U.S.C. 103(a) as being independently unpatentable over DE 2062001 (1970) and JP 4193867. The references teach a generic group of 4-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives which embrace Applicants' claimed compounds and as well as uses. See, in DE 2062001, formula (I) on page 1 and definitions of substituents R¹-R⁴. In CH 538477, see formula (I) and the definition of variable X¹, X², and R¹. The instant claims differ from these references by reciting specific species and a more limited genus (or subgenus) than the reference. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Claims 30, 33, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trepanier *et al.* (J. Med. Chem., 16, 342-347, 1973), CA 2015114

(1989), and Miller *et al* (Synthetic Communications, 24, 1187-1193, 1994). The reference of Trepanier teaches, for example, 2,3,8-trimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline which differs only by an extra methyl group of the compound 2,8-dimethyl-4-phenyl-1,2,3,4-tetrahydro-isoquinoline recited in claim 30. The reference CA 2015114 teaches 4-(4-fluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (see claim 3 in the said reference) which differs only by a methyl group of the compound 2,7-dimethyl-4-(4-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline recited in claim 30 of the instant application. The reference of Miller *et al* teaches 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (see page 1192, paragraph 2) which differs only by a methyl group at C-7 position of the compound 2,7-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline recited in claim 30 of the instant application.

Applicants are advised to note that compounds that differ only by the presence of an extra methyl group are homologues. Homologues (includes those excluded by proviso) are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. The homologue is expected to be preparable by the same method and to have the same properties. This expectation is then deemed the motivation for preparing homologues. Homologues are obvious even in the absence of a specific teaching to introduce methyl group. *In re Wood* 199 USPQ 137; *In re Hoke* 195 USPQ 148; *In re Lohr* 137 USPQ 548; *In re Magerlein* 202 USPQ 473; *In re Wiechert* 152 USPQ 249; *Ex parte Henkel* 130 USPQ 474; *In re Fauque* 121 USPQ 425; *In re Druey* 138 USPQ 39. In all of these cases, the close structural similarity of

two compounds differing by only one (or two) methyl groups sufficed; no specific teaching to introduce a methyl group was present or required. None of these cases has been overruled and indeed the examiner is unaware of any post Lohr case in which motivation is required to put a methyl group on an old compound.

Claims 30, 33, and 34 are also rejected under 35 U.S.C. 103 (a) as being unpatentable over Tirelli *et al.* Note that compounds embraced by the instant claims (including those excluded by proviso) that are ring position isomers are rendered obvious by the reference. See, for example, 4-(3,4-dichloro)phenyl-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline recited in claim 29. The said compound is a positional isomer of 4-(3,4-dichloro)phenyl-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline taught by by Tirelli *et al.*

Claim Rejections – 35 U.S.C. 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-36, 43-47, and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i). "A compound of the formula **IA-IF** having the following structure" recited in claim 1 is an improper Markush language. A correction to "A compound of formula **I (A-F)**" is suggested.

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ii). In claim 1, there is no description of substituents present on structures **IC** and **ID** (see line 13 and 15 on claims page 2). Correction is requested.

iii). The compounds (2-methyl-4-phenyl-7-isoquinoliny)-N-methylmethaneamine and N-methyl (2-methyl-4-phenyl-7-isoquinoliny)-N-methylmethaneamine recited in claim 29 have no antecedent basis in claim 1. This makes claims 30, 33, and 34 indefinite. Appropriate correction is requested.

iv). The compound (3,5-difluoro)-4-phenyl-1,2,7-trimethyl-1,2,3,4-tetrahydroisoquinoline recited in claim 30 does not exist. Appropriate correction to the naming of the said compound is requested.

v). The term "solvate" recited in claims 1 and 30 makes claims 1-36, 43-47, and 49 indefinite. The specification (page 6, line 32) cites an example of solvate as "hydrates". The specification is open-ended and, therefore, the claims that recite the phrase "solvate" have the same unascertainable scope. Removal of term "solvate" is suggested to overcome this objection.

vi). In claim 24, the definition of R^3 includes hydrogen. There is no antecedent basis for this in claim 23. Appropriate correction is requested.

vii). The phrases "selected from table C" and "wherein the enantiomer is selected from table D" make claims 31 and 32 indefinite. Note that a claim must recite all the limitations and not refer to the specification. Appropriate corrections are requested.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36, 43-47, and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The term "prodrug" recited in claims 1 and 29 embraces various classes of unspecified functional groups regardless of complexity of structure or selective location on the site of the parent compound for which there is no sufficient enabling disclosure by way of working examples or sources of starting materials is disclosed. The citation of a standard text on page 8 (lines 32-35) and 9 (lines 1-7) in the specification cannot be considered as enablement for prodrug(s). The possibilities are non-limiting and thus more than routine experimentation would be required to identify and prepare suitable prodrug candidates. As far as the examiner is aware, it could include general classes of derivatives such as esters, amides, and peptide conjugates and the choice of derivatives as suitable produgs requires extensive testing for the rate of cleavage as well as *in vivo* stability, both of which are functions of the parent drug.

Claim 29 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claim recites "a radiolabel led compound of claim 1" for which there is written description.

Regarding enablement for chemical cases, the M.P.E.P. explicitly states that:

.....in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. **In re Soll**, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most **chemical reactions** and physiological activity, more may be required. **In re Fisher**, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also **In re Wright**, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); **In re Vaeck**, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is **not obvious** from the disclosure of one species, what other species will work. {M.P.E.P. 2164.03}

Also, as has been ruled by the court in *Genentech Inc. v. Novo Nordisk*, failure to disclose any specific starting material or any condition for preparation constitutes lack of enablement. Thus, relying on the knowledge of one skilled in the art cannot cure deficiency in enablement (**Genentech Inc. v. Novo Nordisk**, 108 F.3d 1361, 42 USPQ 2d 1001 (Fed. Cir. 1977)).

Information Disclosure Statement

Applicants are requested to provide a copies of Bundgard (A Textbook of Drug Design and Development), Geene *et al.* (Protective Groups in Organic Synthesis), McComie (Protective Groups in Organic Chemistry), cited in their IDS for consideration. Applicants are advised to let the Examiner know of the relevance of the reference EP 0 599 538 A1 cited in their IDS (paper #3).


Any inquiry concerning this communication from the examiner should be directed to Rao M. Uppu whose telephone number is (703) 308-3951. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund J. Shah, can be reached on (703) 308-4716. The fax number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Rao M. Uppu, Ph.D.
Examiner
Art Unit 1624


BRUCK KIFLE, PH.D.
PRIMARY EXAMINER

 Mukund Shah
Supervisory Examiner
Art Unit 1624